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(54) Title: SURFACTANT FREE TOPICAL COMPOSITIONS AND METHOD FOR RAPID PREPARATION THEREOF

(57) Abstract: The present invention relates to a composition for topical, oral, nasal, anal, ophthalmic, or vaginal application comprising a base composition and at least one dispersion comprising suspended particles of a hydrophobic active agent, a hydrophobic adjuvant, or a combination thereof. The base composition comprises a rheology modifying agent and water. The composition is substantially free of emulsifying surfactants and the suspended particles generally have a diameter less than about 500 or 1,000 nm. Another embodiment is a method of preparing a composition comprising mixing the aforementioned base composition with the aforementioned dispersion. Mixing may be performed with a propeller mixer or manually,*i.e.*, by hand. Since the topical dispersion is simple and quick to prepare, custom cosmetic compositions may be prepared at the point of sale for customers. Prior to the present invention, such products would take hours to be prepared. Furthermore, the method of the present invention is significantly more efficient *i.e* less expensive and faster) than conventional methods for preparing emulsion-based compositions. The present invention further relates to a method of treating topical, oral, nasal, anal, ophthalmic or vaginal disorders with the composition of this invention.

SURFACTANT FREE TOPICAL COMPOSITIONS AND METHOD FOR RAPID PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to surfactant free topical compositions and a rapid method for the preparation of the same.

BACKGROUND OF THE INVENTION

Most topical preparations currently sold contain a wide variety of physiologically active agents and/or aesthetic modifying agents. Physiologically active agents are compounds which cause a physical change to the body following their application. Examples of such agents include alpha hydroxy acids, antioxidants, and vitamins. Aesthetic modifying agents provide the composition with a defined physical characteristic such as, for example, the degree of moisturization, oil content, and physical form of the composition. Some examples of aesthetic modifying agents include silicone fluids and derivatives, waxes, botanical (vegetable) oils, hydrocarbon-based oils, esters and fragrances.

The performance of these active agents is dependent upon the vehicle used to deliver them. These vehicles range from simple solvents, such as water and ethanol, to complex emulsions. Unfortunately not all active agents are completely soluble or compatible with all vehicles. For example, oil soluble active agents are typically not compatible with water or water-based gel vehicles. As a result, many

such products exhibit poor delivery of active agents, have poor tactile properties, or are thermodynamically unstable and result in a commercially unacceptable shelf life.

Topical preparations having a non-water based solvent are typically not cosmetically elegant, *i.e.*, they do not have an aesthetically pleasing appearance, feel, and/or fragrance. Furthermore, non-water based solvents can cause unwanted side effects, such as irritation or damage to the epithelial surface to which they are applied.

To avoid the problems associated with water and non-water based solvents, stable emulsions are commonly employed to deliver physiologically active agents and aesthetic modifying agents. These emulsions form either spherical micelles of one or more hydrophobic liquid materials in water or spherical droplets of water in a hydrophobic fluid. Such emulsions are typically formed by separately preparing an oil phase and a water phase and mixing the two phases together. In other words, the hydrophobic ingredients are dissolved in a suitable oil phase and the hydrophilic ingredients are dissolved in water. The two phases are then combined with one or more emulsifying agents which are incorporated into either or both the water and oil phases. The emulsifying agents reduce the surface tension between the oil and water phases, thereby making the combination of the two phases more stable.

Such emulsions are generally prepared by heating the oil and water phases to a temperature of 70° C or greater before combining them. The oil and water phases are combined and then slowly cooled to ensure the formation of crystalline structures which enhance the stability of the emulsion. These emulsions usually have a homogeneous opaque white appearance and a smooth or pleasant feeling upon application to the skin or other epithelial surface. However, the use of such emulsions to delivery physiological and/or aesthetic benefits has many limitations.

The presence of significant amounts of surfactant can strip the material lipid barrier of the skin or the lipid bilayer of epithelial cell membranes leaving the tissue vulnerable. Thus, the surfactants themselves can evoke an

irritation. Furthermore, the damaged barrier permits the passage of other materials that can cause irritation or increase skin sensitivity and allergic reactions. The literature is replete with clinical evidence of the damaging consequences that can occur with the use or overuse of surfactants. For example, Effendy I., Maibach H.I., "Surfactants and experimental irritant contact dermatitis", *Contact Dermatitis*, 33(4);217-25 (10/1995), indicates that "[m]any surfactants elicit irritant reactions when applied to the skin, partially due to their relative ability to solubilize lipid membranes." Barany E., Lindberg M., Loden M., "Biophysical characterization of skin damage and recovery after exposure to different surfactants", *Contact Dermatitis* 40(2):98-103 (2/1999), states that "[t]he majority of adverse skin reactions to personal care products are presumed to be caused by irritant substances, like surfactants."

Moreover, there are limitations to conventional topical preparations. For example, many materials having aesthetic properties are not easily incorporated into an emulsion, such as, for example, fluorinated compounds. Additionally, each time the oil or water phase is changed in a formulation, the amount and type of emulsifying agents in the formulation needs to be readjusted.

Many topical preparations formulated contain active agents and/or aesthetic modifying agents which readily become destabilized in emulsions, causing them to degenerate and/or deteriorate. For example, prolonged heating of the water and oil phases can thermodynamically modify the active agent or can kinetically accelerate the reaction of the active agent with another agent in the emulsion or with air if the material is oxygen sensitive.

Moreover, lowering the surface tension of a topical preparation generally increases the surface exposure of the active agent or aesthetic modifying agent to oxygen and other destabilizing materials. For example, in a topical preparation containing retinol as an active ingredient, the instability of the preparation may decrease the efficacy of the retinol. The instability of an unsaturated

fatty acid as an aesthetic modifying agent leads to color changes in the preparation and malodor.

Since the time between manufacturing and sale of a cosmetic product is typically several weeks, the product is often no longer "fresh" or effective since the active agent has degenerated or deteriorated. To offset instability problems, many other materials such as chelating agents, antioxidants and masking agents are usually included in the formulation.

Typical emulsions are time consuming to prepare, require heating, are produced in multiple phases, are slow cooling, and often require high shear conditions to get the particle size small enough for maximum stability. Larger batches may require 8 to 24 hours to process and can take several days to set up. It is also often difficult to control the process parameters for preparing the emulsion. If any factors such as the heating, cooling or mixing rates are not carefully duplicated, the preparation may have different properties than the preceding batches of the same product. As a result, the stability of the emulsion may vary from batch to batch. Often the difference of a single parameter is significant enough to cause the product to be outside the established optimum specifications. These batches then have to be either discarded or re-worked.

The lack of reproducibility is especially problematic when the product contains a physiologically active agent. Lack of reproducibility can effect product performance and end user satisfaction. The lack of reproducibility also results in products having different aesthetic properties which the end user will perceive as a lack of quality and will ultimately lead to consumer dissatisfaction or reduced compliance.

Emulsions are typically expensive to manufacture. This is due to a variety of factors including the energy to heat the batch, the specialized equipment required to process the emulsion, such as specialized pumps and cooling/heating equipment, and the time the process ties up equipment and personnel. Moreover, such emulsions cannot be easily processed or customized at the point of purchase.

Since most skin care medicaments are prepackaged and have predetermined dosages, dermatologists cannot readily administer to patients varying dosages of these medicaments. As a result, a patient may need to apply two or more different skin care preparations since a single preparation with all of the prescribed medicaments may not be available.

Some dermatologists prepare their own skin care preparations. These skin care preparations typically have poor aesthetic properties resulting in poor patient compliance. Thus, it would be desirable for dermatologists to be able to quickly and easily prepare skin care preparations having varying dosages of medicaments and an aesthetically pleasing appearance.

Present cosmetic products contain predetermined amounts of active agents. Customers cannot pick and choose which ingredients to include in these products. Many customers do not purchase certain cosmetic products because of an allergic reaction with one or more of the ingredients included in the product. For example, many customers are allergic to various fragrances. It would therefore be advantageous to prepare the cosmetic product at the point of sale without the fragrances. Also, customers may have to apply two or more different cosmetic products to get a desired effect since a single product with the desired combination of active agents and/or aesthetic modifying agents may not be on the market. Many cosmetic products are sold in only one form, such as a spray, gel or lotion. Customers, however, may prefer other forms of the cosmetic product.

Prior to the present invention, it was not practical to prepare custom cosmetic products at the point of sale. The preparation of most current cosmetic products require heating, other energy expensive processes, and/or large industrial equipment. As a result, it was not economically feasible to prepare custom cosmetic products at the point of sale. Furthermore, active ingredients which are heat sensitive and oil soluble could not readily be incorporated into cosmetic products by conventional heating without partially or completely degrading the active ingredient.

For the foregoing reasons, there is a need for a substantially surfactant free cosmetic product which can be prepared at the point of sale. Also, there is a need for a method of preparing such a cosmetic product which is fast and does not require heating or other expensive processing techniques.

SUMMARY OF THE INVENTION

The present invention relates to a composition for topical, oral, nasal, anal, ophthalmic, or vaginal application comprising a base composition and at least one dispersion comprising suspended particles of a hydrophobic active agent, a hydrophobic adjuvant, or a combination thereof. The base composition comprises a rheology modifying agent and water. The composition is substantially free of emulsifying surfactants. The suspended particles generally have a diameter less than about 500 or 1,000 nm.

Another embodiment is a method of preparing a topical dispersion comprising mixing the aforementioned base composition with the aforementioned dispersion. Mixing may be performed with a propeller mixer or manually, *i.e.*, by hand. Preferably, the base composition is premanufactured. Since the topical dispersion is simple and quick to prepare, custom cosmetic ecompositions may be prepared at the point of sale for customers in minutes. Prior to the present invention, such products would take hours to be prepared.

The present invention further relates to a method of preparing a composition for topical, oral, nasal, anal, ophthalmic, or vaginal application comprising mixing a base composition with at least one dispersion comprising suspended particles of a hydrophobic active agent, a hydrophobic adjuvant, or a combination thereof. The base composition comprises a rheology modifying agent and water. Preferably, the base composition is premanufactured. Thecomposition is substantially free of emulsifying surfactants and the suspended particles have a diameter less than about 500 or 1000 nm. Mixing may be performed with a propeller mixer or manually, *i.e.*, by hand using a spatula or other similar device. Since the

composition is simple and quick to prepare, custom cosmetic compositions may be prepared at the point of sale for customers in minutes. Prior to the present invention, such products would take hours to be prepared. Furthermore, the method of the present invention is significantly more efficient (*i.e.* less expensive and faster) than conventional methods for preparing emulsion-based compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a flowchart generally illustrating the method according to one aspect of the invention;

Fig. 2 is a block diagram of a system for implementing the method; and

Fig. 3 is a flowchart generally illustrating the method according to this aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of preparing a composition for topical, oral, nasal, anal, ophthalmic, or vaginal application comprising mixing a base composition with at least one dispersion comprising suspended particles of a hydrophobic active agent, a hydrophobic adjuvant, or a combination thereof. The base composition comprises a rheology modifying agent and water.

The base composition is premanufactured, *i.e.*, prepared at a location remote from where the mixing step is performed or prepared in large quantities. The term "large quantities" is herein defined as a quantity greater than that needed to produce a single final product and is preferably many multiples times that. The base composition is typically premanufactured in large batches. When the base composition is prepared at a location remote from where the mixing step is performed, it may be dehydrated to form a dry powder or gel in order to decrease transportation costs and ease transport and hydrated at the location where the mixing step is performed.

Other active agents and adjuvants, such as those described in *Remington's Pharmaceutical Sciences*, 19th Edition, A. R. Gennaro (1995) and the *International Cosmetic Ingredient Dictionary and Handbook*, 7th Edition (1997), published by The Cosmetic, Toiletry, and Fragrance Association (both of which are hereby incorporated by reference), may be mixed with the base composition and dispersion.

Generally, essentially all hydrophobic ingredients to be included in the final composition are added as dispersions (*i.e.* a dispersion of the hydrophobic ingredient is prepared before it is mixed with the base composition and the dispersion). Without being bound by any theory, it is believed that the suspended particles in the dispersions made essentially without surfactants have a charge at their surface resulting from the processing conditions needed to make the dispersions. These mini cells (suspended particles) tend to repel one another. Mini cells made with two or more oils will also not interact because of the repulsive force.

Mixing is generally performed at a temperature of from about 15 to about 30° C, preferably at a temperature of from about 20 to about 30° C, and most preferably at ambient temperature. Since the hydrophobic active agent or hydrophobic adjuvant is added to the base composition as a dispersion, heating and other expensive processing steps are not required to obtain a homogenous final composition. Preferably, the composition is not heated during preparation. Generally, mixing is performed at ambient pressure.

Emulsifying surfactants are preferably not added to the composition. As a result, the composition is substantially free of emulsifying surfactants. The composition preferably comprises less than about 3% by weight and more preferably less than about 1% by weight of emulsifying surfactants, based upon 100% weight of total composition.

The composition may be prepared as a cream, gel, lotion, serum or spray.

Since the method of the present invention may be used to rapidly prepare new formulations (*e.g.* within 5-10 minutes), it can be applied to decrease the

cycle time for formulating and manufacturing new formulations. Most typical emulsion-based formulations take hours to be prepared. Additionally, manufacturing formulations according to the method of the present invention is significantly less expensive than conventional manufacturing techniques for emulsion-based compositions. The method of the present invention is particularly applicable to combinatorial methods of formulating.

The present invention further relates to a composition for topical, oral, nasal, anal, ophthalmic, or vaginal application comprising a base composition and at least one dispersion comprising suspended particles of a hydrophobic active agent, a hydrophobic adjuvant, or a combination thereof. The base composition comprises a rheology modifying agent and water. The composition is substantially free of emulsifying surfactants. The suspended particles generally have a diameter less than about 500 or 1,000 nm.

The composition is substantially free of emulsifying surfactants. The composition preferably comprises less than about 3% by weight and more preferably less than about 1% by weight of emulsifying surfactants, based upon 100% weight of total composition.

The composition of the present invention may be prepared by mixing the base composition with the dispersion containing at least one of a hydrophobic active agent or a hydrophobic adjuvant. Preferably, the base composition is premanufactured, *i.e.*, prepared at a location remote from where the mixing step is performed or prepared in large quantities. The term "large quantities" is herein defined as a quantity greater than that needed to produce a single final product and is preferably many multiples times that. The base composition is typically premanufactured in large batches.

The dispersion is generally a homogenous fluid which is stable for a commercially relevant period of time. The dispersion typically remains stable for at least 2 weeks and preferably at least 2 months.

According to a preferred embodiment, the dispersion is prepared by mixing from about 0.1% to about 70% by weight of hydrophobic active agent and/or hydrophobic adjuvant with from about 30% to about 99.9% by weight of aqueous phase under high pressure and high shear conditions, based upon 100% weight of total dispersion. The aqueous phase contains water and, optionally, other hydrophilic adjuvants. More preferably, the mixing is performed with shearing at a pressure of from about 9,000 to about 25,000 psi to form a dispersion having an average particle size ranging from about 50 to about 500 nm.

The present invention further relates to a method for treating topical, oral, nasal, anal, ophthalmic or vaginal disorders with the composition of the present invention.

Rheology Modifying Agents

The base composition comprises a rheology modifying agent and water.

Rheological modifying agents within the scope of the invention include any substance which increases or decreases the viscosity of the sunscreen formulation. Suitable rheology modifying agents include, but are not limited to, phosphorylated starch derivative, carbohydrate based rheology modifying agents, polymeric and copolymeric rheology modifying agents, inorganic rheology modifying agents, protein rheology modifying agents, polypeptide rheology modifying agents, and any combination of any of the foregoing.

The term "phosphorylated starch derivative" includes, but is not limited to, starches containing a phosphate group. Suitable phosphorylated starch derivatives include, but are not limited to, hydroxyalkyl starch phosphates, hydroxyalkyl distarch phosphates, and any combination of any of the foregoing. Non-limiting examples of hydroxyalkyl starch phosphates and hydroxyalkyl distarch phosphates include hydroxyethyl starch phosphate, hydroxypropyl starch phosphate,

hydroxypropyl distarch phosphate (including sodium hydroxypropyl starch phosphate), and any combination of any of the foregoing.

Non-limiting examples of suitable carbohydrate based rheology modifying agents include algin and derivatives and salts thereof, such as algin, calcium alginate, propylene glycol alginate, and ammonium alginate; carrageenan (*Chondrus crispus*) and derivatives and salts thereof, such as calcium carrageenan and sodium carrageenan; agar; cellulose and derivatives thereof, such as carboxymethyl hydroxyethylcellulose, cellulose gum, cetyl hydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, and cellulose gum; chitosan and derivatives and salts thereof, such as hydroxypropyl chitosan, carboxymethyl chitosan, and chitin; gellan gum; guar (*Cyanopsis tetragonoloba*) and derivatives thereof, such as guar hydroxypropyltrimonium chloride and hydroxypropyl guar; hyaluronic acid and derivatives thereof, such as sodium hyaluronate; dextran and derivatives thereof; dextrin; locust bean (*Ceratonia siliqua*) gum; mannans and derivatives thereof, such as C_{1-5} alkyl galactomannan; starches, such as starch polyacrylonitrile copolymer-potassium salt and starch polyacrylonitrile copolymer-sodium salt; pectin; sclerotium gum; tragacanth (*Astragalus gummifer*) gum; xantham gum and derivatives thereof; and any combination of any of the foregoing.

Non-limiting examples of suitable polymeric and copolymeric rheology modifying agents include acrylates, methacrylates, polyethylene and derivatives thereof, and any combination of any of the foregoing. Suitable acrylates and methacrylates include, but are not limited to, carbomer and derivatives and salts thereof, acrylate/C_{10}-C_{30} alkyl acrylate crosspolymer, acrylate/ceteth-20 itaconate copolymer, acrylate/ceteth-20 methacrylate copolymers, acrylate/steareth-20 methacrylate copolymers, acrylate/steareth-20 itaconate copolymers, acrylate/steareth-50 acrylate copolymers, acrylate/VA crosspolymers, acrylate/vinyl isodecanoate crosspolymers, acrylic acid/acrylonitrogen copolymers, ammonium acrylate/acrylonitrogen copolymers, glyceryl polymethacrylate, polyacrylic acid,

PVM/MA decadiene crosspolymer, sodium acrylate/vinyl isodecanoate crosspolymers, sodium carbomer, ethylene/acrylic acid copolymer, ethylene/VA copolymer, acrylate/acrylamide copolymer, acrylate copolymers, acrylate/hydroxyester acrylate copolymers, acrylate/octylarylamide copolymers, acrylate/PVP copolymers, AMP/acrylate copolymers, butylester of PVM-MA copolymer, carboxylate vinylacetate terpolymers, diglycol/CHDM/isophthalates/SIP copolymer, ethyl ester of PVM-MA copolymer, isopropyl ester of PVM-MA copolymer, octylacrylamide/acrylate/butylaminoethyl methacrylate copolymers, polymethacrylamidopropyltrimonium chloride, propylene glycol oligosuccinate, polyvinylcaprolactam, PVP, PVP/dimethylaminoethylmethacrylate copolymer, PVP/DMAPA acrylate copolymers, PVP/carbamyl polyglycol ester, PVP/VA copolymer, PVP/VA vinyl propionate copolymer, PVP/vinylcaprolactam/DMAPA acrylate copolymers, sodium polyacrylate, VA/butyl maleate/isobornyl acrylate copolymers, VZ/crotonates copolymer, VA/crotonates vinyl neodecanoate copolymer, VA crotonates/vinyl propionate copolymer, vinyl caprolactam/PVP/dimethylaminoethylmethacrylate copolymer, and any combination of any of the foregoing.

Non-limiting examples of suitable inorganic thickening agents include clays and derivatives thereof, silicates, silicas and derivatives thereof, and any combination of any of the foregoing. Suitable clays and derivatives thereof include, but are not limited to, bentonite and derivatives thereof, such as quaternium-18 bentonite; hectorite and derivatives thereof, such as quaternium-18 dectorite; montmorillonite; and any combination of any of the foregoing. Suitable silicates include, but are not limited to, magnesium aluminum silicate, sodium magnesium silicate, lithium magnesium silicate, tromethamine magnesium aluminum silicate, and any combination of any of the foregoing. Suitable silicas and derivatives thereof include, but are not limited to, hydrated silica, hydrophobic silica, and any combination of any of the foregoing.

Suitable protein and polypeptide rheology modifying agents include, but are not limited to, proteins and derivatives and salts thereof, polypeptides and derivatives and salts thereof, and any combination of any of the foregoing. Non-limiting examples of protein and polypeptide rheology modifying agents include albumin, gelatin, keratic and derivatives thereof, fish protein and derivatives thereof, milk protein and derivatives thereof, wheat protein and derivatives thereof, soy protein and derivatives thereof, elastin and derivatives thereof, silk protein and derivatives thereof, and any combination of any of the foregoing.

Preferred rheology modifying agents include, but are not limited to, carbomer, acrylate/alkyl acrylate crosspolymers, acrylate/vinyl isododecanoate crosspolymer, xantham gum, locust bean gum, guar gum, and any combination of any of the foregoing. A more preferred combination of rheology modifying agents comprises carbomer and an acrylate/alkyl acrylate copolymer, such as an acrylate/C_{10}-C_{30} alkyl acrylate crosspolymer. According to the International Cosmetic Ingredient Dictionary and Handbook (7^{th} Ed., The Cosmetic, Toiletry, and Fragrance Association), carbomer is a homopolymer of acrylic acid crosslinked with an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene. The term "acrylate/alkyl acrylate crosspolymer" includes, but is not limited to, copolymers of alkyl acrylates with one or more monomers of acrylic acid, methacrylic acid, or one of their short chain (i.e. C_{1-4} alcohol) esters, wherein the crosslinking agent is, for example, an allyl ether of sucrose or pentaerytritol. Preferably, the alkyl acrylates are C_{10}-C_{30} alkyl acrylates. Examples of such copolymers include, but are not limited to, those commercially available as Carbopol™ 1342, Carbopol™ 1382, Pemulen™ TR-1, and Pemulen™ TR-2, from Goodrich Specialty Chemicals of Cleveland, OH.

Preferred rheological modifying agents include, but are not limited to hydrophilic gelling agents, such as carboxyvinyl polymers (carbomer), acrylic copolymers (*e.g.* acrylate/alkyl acrylate copolymers), polyacrylamides,

polysaccharides (*e.g.* hydroxypropylcellulose), natural gums, clays, and any combination of any of the foregoing.

Preferably, the cosmetic base contains at least two different rheology modifying agents. Preferred combinations of rheology modifying agents include, but are not limited to, hydroxypropyl distarch phosphate and carbomer; guar hydroxypropyltrimonium chloride and hydroxypropyl guar; sodium hydroxypropyl starch phosphate and carbomer; and hydroxypropyl methylcellulose and pectin.

Generally, the final base composition contains from about 0.01 to about 35% by weight, preferably from about 0.4 to about 10% by weight, and more preferably from about 0.4 to about 6% by weight of the rheological modifying agent, based upon 100% weight of total composition. Typically, the rheology modifying agent is combined with water or water plus, a water soluble cosolvent. The base composition may be prepared by methods known in the art.

The base composition preferably contains a preservative.

Hydrophobic Active Agent or Hydrophobic Adjuvant Dispersion

A hydrophobic active agent or hydrophobic adjuvant of the present invention is an active agent or adjuvant which has a non polar property which makes it essentially insoluble in water or water and polar solvent solution. Hydrophobic active agents and hydrophobic adjuvants of the present invention include, but are not limited to, partially and fully hydrophobic active agents and partially and fully hydrophobic adjuvants. For example, hydrophobic active agents encompassed by the present invention include compounds and complexes which contain a hydrophobic moiety. The dispersion is generally a homogenous fluid which is stable for a commercially relevant period of time. The dispersion typically remains stable for at least 2 weeks and preferably at least 2 months

The composition of the present invention may also include non-hydrophobic active agents and non-hydrophobic adjuvants.

The dispersion containing the suspended particles generally contains from about 0.01 to about 70% by weight of oil, based upon 100% weight of total dispersion. Preferably, the dispersion contains from about 1.0 to about 50% by weight of oil, based upon 100% weight of total dispersion. The oil component of the composition may include active agents and adjuvants which are oils.

The dispersion is a suspension of liquid or solid particles of colloidal size or larger in a liquid medium. Generally, the dispersion contains suspended particles, such as oil particles (or oil droplets), having a diameter greater than about 1000 nm. The diameter of the suspended particles preferably ranges from about 50 nm to about 500 nm and more preferably from about 250 to about 500 nm. Preferably, the oil droplets contain one or more lipophilic materials. The oil droplets may have a charge as determined by zeta potential measurements. The oil droplets may be prepared by microfluidzation or ultra high shear mixing, such as that described in U.S. Patent No. 6,159,442, which is hereby incorporated by reference. Preferred oil containing dispersions are sold under the tradename Sansurf™ by Collaborative Laboratories, Inc. of East Setauket, NY. And Dermasomes□ by Microfluidics Corp. of Newton, MA.

According to a preferred embodiment, the dispersion is prepared by mixing from about 0.1% to about 70% by weight of hydrophobic active agent and/or hydrophobic adjuvant with from about 30% to about 99.9% by weight of aqueous phase under high pressure, high shear or high pressure and high shear conditions, based upon 100% weight of total dispersion. The aqueous phase contains water and, optionally, other hydrophilic adjuvants. More preferably, the mixing is performed with shearing at a pressure of from about 9,000 to about 25,000 psi to form a dispersion having an average particle size ranging from about 50 to about 500 nm.

Active Agents

Suitable active agents include, but are not limited to, anti-acne agents, antimicrobial agents, antiinflammatory agents, analgesics, antietythemal agents,

antipruritic agents, antiedemal agents, antipsoriatic agents, antifungal agents, skin protectants, sunscreen agents, vitamins, antioxidants, scavengers, antiirritants, antibacterial agents, antiviral agents, antiaging agents, protoprotection agents, hair growth enhancers, hair growth inhibitors, hair removal agents, antidandruff agents, anti-seborrheic agents, exfoliating agents, wound healing agents, anti-ectoparacitic agents, sebum modulators, immunomodulators, hormones, botanicals, moisturizers, astringents, sensates, antibiotics, anesthetics, steroids, tissue healing substances, tissue regenerating substances, amino acids, ceramides, and any combination of any of the foregoing.

Preferred anti-acne agents include, but are not limited to, salicylic acid, retinoic acid, alkyl alpha hydroxy acid, benzyl peroxide, sodium sulfacetamide, clindamycin, and any combination of any of the foregoing. Preferred combinations of anti-acne agents to be incorporated in the composition include salicylic acid and retinoic acid; sodium sulfacetamide and clindamycin; salicylic acid and clindamycin; salicylic acid, alkyl alpha hydroxy acid, and tetrahydrozoline.

Suitable antimicrobial agents include, but are not limited to, benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, chloroxylenol, cloflucarban, fluorosalan, hexachlorophene, hexylresorcinol, iodine complex, iodine tincture, para-chloromercuriphenol, phenylmercuric nitrate, thimerosal, vitromersol, zyloxin, triclocarban, triclosan, methyl-benzethonium chloride, nonyl phenoxypoly(ethyleneoxy) ethanol-iodine, para-chloro-meta-xylenol, triclorcarban, undecoylium chloride-iodine complex, and any combination of any of the foregoing.

Suitable antiinflammatory agents include, but are not limited to, alidoxa, allantoin, aloe vera, aluminum hydroxide, bismuth subnitrate, boric acid, calamine, casein, cellulose, microporous, cholecatciferol, cocoa butter, cod liver oil, colloidal oatmeal, dexpanthenol, dimethicone, glycerin, kaolin, lanolin, live yeast cell derivative, mineral oil, peruvian balsam, petrolatum, protein hydrolysate, racemethionine, shark liver oil, sodium bicarbonate, sulfur, talc, tannic acid, topical

starch, vitamin A, vitamin E, white petrolatum, zinc acetate, zinc carbonate, zinc oxide, hydrocortisone, betamethasone, ibuprofen, indomethicin, acetyl salicylic acid, tacrolimus, flucoinolone acetonide, sodium sulfacetamide, and any combination of any of the foregoing.

Suitable analgesics include, but are not limited to, diphenhydramine, tripelennamine, benzocaine, dibucaine, lidocaine, tetracaine, camphor, menthol, phenol, resorcinol, matacresol, juniper tar, methylsalicylate, turpentine oil, capsicum, methyl nicotinate, b-glucan, and any combination of any of the foregoing.

Suitable antietythermal agents include, but is not limited to, tetrahydrozoline and hydracortisone.

Suitable antipruritic agents include, but are not limited to, benadryl, pramoxine, antihistamines, and any combination of any of the foregoing.

Suitable antiedemal agents, include, but are not limited to, pregnenalone acetate, tanin glyrosides, and any combination of any of the foregoing.

Suitable antipsoriatic agents include, but are not limited to, caleipotriene, coal tar, anthralin, vitamin A, and any combination of any of the foregoing. Preferred combinations of antipsoriatic agents include, but are not limited to, hydrocortisone, retinoic acid, and alkyl alpha hydroxy acid; dovonex, salicylic acid, and a sunscreen agent; indomethicin, salicylic acid, and urea; anthralin and salicylic acid; and anthralin and indomethicin. Other suitable antipsoriatic agents include, but are not limited to, caleipotriene, coal tar, anthralin, vitamin A, and any combination of any of the foregoing.

Suitable antifungal agents include, but are not limited to, clioquinol, haloprogin, miconazole nitrate, clotrimazole, metronidazole, toinaftate, undecylenic acid, iodoquinol, and any combination of any of the foregoing.

Suitable skin protectants include, but are not limited to, cocoa butter, dimethicone, petrolatum, white petrolatum, glycerin, shark liver oil, allantoin, and any combination of any of the foregoing.

Suitable sunscreen agents include, but are not limited to, ethylhexyl methoxycinnamate, avobenzone, benzophenone-3, octacrylene, titanium dioxide, zinc oxide, and any combination of any of the foregoing.

Suitable antioxidants include, but are not limited to, scavengers for lipid free radicals and peroxyl radicals, quenching agents, and any combination of any of the foregoing. Suitable antioxidants include, but are not limited to, tocopherol, BHT, beta carotene, vitamin A, ubiquinol, ferulic acid, azelaic acid, thymol, catechin, sinapic acid, lactoferrin, rosmariquinone, hydroxytyrosole, sesamol, 2-thioxanthine, nausin, malvin, carvacone, chalcones, glutathione isopropyl ester, xanthine, melanin, guanisone, lophorphyrins, 8-hydroxyxanthine, 2-thioxanthione, vitamin B_{12}, plant alkaloids, catalase, quercetin, tyrosine, SOD, cysteine, methionine, genistein, NDG, procyanidin, hamamelitannin, ubiquinone, trolox, licorice extract, propyl gallate, sinapic acid, and any combination of any of the foregoing.

Suitable vitamins include, but are not limited to, vitamin E, vitamin A palmitate, vitamin D, vitamin F, vitamin B_6, vitamin B_3, vitamin B_{12}, vitamin C, ascorbyl palmitate, vitamin E acetate, biotin, niacin, DL-panthenol, and any combination of any of the foregoing.

A preferred sunscreen agent is a mixture of ethylhexyl methoxycinnamate, butyl methoxydibenzoylmethane, and water, and is available as Solarease™ from Collaborative Laboratories, Inc. of East Setauket, NY.

Suitable amino acids include, but are not limited to, glycine, serine, and any combination of any of the foregoing.

Aesthetic Modifying Agents

The composition preferably includes at least one aesthetic modifying agent. An aesthetic modifying agent is a material which imparts desirable tactile, olfactory, taste or visual properties to the surface to which the composition is applied. The aesthetic modifying agent may be hydrophobic or hydrophilic. The

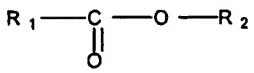
aesthetic modifying agent is preferably hydrophobic and is more preferably an oil, wax, solid or paste.

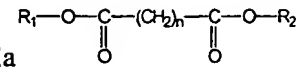
A dispersion of one or more hydrophobic aesthetic modifying agents is preferably prepared before the hydrophobic aesthetic modifying agents are incorporated into the composition. The hydrophobic aesthetic modifying agents may be dispersed into an aqueous phase by methods, such as ultra high shear mixing and microfluidization.

The final composition may be prepared by mixing the dispersions containing the hydrophobic aesthetic modifying agents with the base composition and any other adjuvants. Since the hydrophobic aesthetic modifying agents are added to the base composition as dispersions, heating and other expensive processing steps are not required to obtain a homogenous final composition.

An example of an aesthetic modifying agent is a mono, di, tri or poly alkyl ester or ether of a di, tri, or polyhydroxy compound, such as ethylene glycol, propylene glycol, glycerin, sorbitol or other polyol compound. Examples of such esters and ethers include, but are not limited to, saturated and unsaturated, linear and branched vegetable oils, such as soybean oil, babassu oil, castor oil, cottonseed oil, chinese tallow oil, crambe oil, perilla oil, danish rapeseed oil, rice bran oil, palm oil, palm kernel oil, olive oil, linseed oil, coconut oil, sunflower oil, safflower oil, peanut oil and corn oil. Preferred saturated and unsaturated vegetable oils are those having fatty acid components with 6 to 24 carbon atoms. A more preferred vegetable oil is soybean oil.

An example of a hydrophobic aesthetic modifying agent is a compound having the formula $C_nH_{(2n+2-m)}$ where n is an integer greater than or equal to 6 and m is 0 or an even integer no greater than n. Such compounds include, but are not limited to, saturated and unsaturated, linear, branched, and cyclic hydrocarbon chains. Preferred examples of such compounds include, but are not limited, mineral oil, petrolatum, permethyl fluids, polybutylenes, and polyisobutylenes.

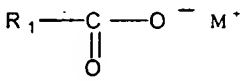
Another example of a hydrophobic aesthetic modifying agent has the formula 

or the formula 

where R_1 is a saturated or unsaturated, linear, branched or cyclic C_1-C_{24} alkyl; R_2 is hydrogen or a saturated or unsaturated, liner, branched or cyclic C_1-C_{24} alkyl; and n is an integer from 0 to 20. Examples of such aesthetic modifying agents include, but are not limited to, isopropyl palmitate and diisopropyl adipate.

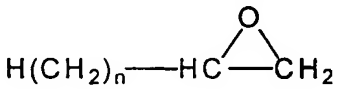
Yet another aesthetic modifying agent is silicone. Silicone may provide lubrication and/or shine to the composition. Preferably, the silicone is insoluble in water. Suitable water-insoluble silicone materials include, but are not limited to, polyalkylsiloxanes, polyarylsiloxanes, polyalkylarylsiloxanes, polysiloxane gums and polyethersiloxane copolymers. Examples of suitable silicone materials are disclosed in U.S. Patent Nos. 4,788,006; 4,341,799; 4,152,416; 3,964,500; 3,208,911; 4,364,837 and 4,465,619, all of which are incorporated herein by reference.

Another suitable hydrophobic material which can be suspended in the composition has the formula



where R_1 is a saturated or unsaturated, linear, branched or cyclic alkyl having 2 to 24 carbon atoms; $M^{(+)}$ is $N^+R_2R_3R_4R_5$; R_2, R_3 and R_4 are hydrogen or a saturated or unsaturated, linear or branched alkyl or hydroxyalkyl having from 1 to 10 carbon atoms; and R_4 is a saturated or unsaturated, linear, branched or cyclic alkyl or substituted alkyl having 2 to 24 carbon atoms. An example of such a material is lauramine oleate.

Another aesthetic modifying agent is a polymer formed by polymerization of alkylene oxide monomers of the formula



where n is an integer from 0 to about 24. The polymer may be either a homogenous polymer or a copolymer. Examples of such homogenous polymers include, but are not limited to, polypropylene oxide and polybutylene oxide. Generally, the molecular weight of these polymers ranges from about 100 to about 10,000 daltons. Additionally, these polymers may be reacted with mono or polyhydroxyalkyl alcohol, such as UCON fluids available from the Union Carbide Chemical Company, or with a saturated or unsaturated, linear, branched or cyclic C_1-C_{24} alkyl.

Other Adjuvants

Other suitable adjuvants include but are not limited to pH adjusters, emollients, conditioning agents, chelating agents, gelling agents, viscosifiers, colorants, fragrances, odor masking agents, UV stabilizer, preservatives, and any combination of any of the foregoing. Preferred pH adjusters include, but are not limited to, aminomethyl propanol, aminomethylpropane diol, triethanolamine, citric acid, sodium hydroxide, acetic acid, potassium hydroxide, lactic acid, and any combination of any of the foregoing.

Suitable conditioning agents include, but are not limited to, cyclomethicone, petrolatum, dimethicone, dimethiconol, silicone, quaternary amines and any combination of any of the foregoing.

The composition preferably contains less than about 0.5% by weight of preservatives, based upon 100% weight of total composition. More preferably, the composition contains from about 0.25 to about 0.5% by weight of preservatives, based upon 100% weight of total composition.

Systems and Methods for Production of Customized Compositions

As will be appreciated by those of skill in the art, because of the long time required to manufacture an adequate base composition for use in pharmaceutical and cosmetic compositions, it has not been considered possible to produce such compositions on demand or in wide variety at a rapid pace. In accordance with a further aspect of the invention, a method and system for producing such a customized composition for using the above described formulations (specific examples of which are given below) or possibly other similar formulations is provided. The method is suitable for manual use, i.e., in a doctor's office, and is also well suited for use in an on-demand customized manufacturing system.

According to a primary element of this aspect of the invention, a base composition comprising a rheology modifying agent and water is provided for use in a pre-mixed format at the manufacturing location. This eliminates the need to

provide specialized mixing equipment at that location and to wait the long period of time (typically several hours) conventionally needed to prepare the base composition. In one embodiment, the base composition can be pre-mixed at the manufacturing location, e.g., in bulk, in advance of an expected manufacturing run. Alternatively, the base composition can be prepared at a location remote from the manufacturing location and delivered in advance. Also provided at the manufacturing location are a plurality of dispersions, each comprising suspended particles of one or more hydrophobic active agents, hydrophobic adjuvants, or combination thereof. Each dispersion has a predefined characteristic or property, such as a medicinal effect. One or more aesthetic modifying agents may also be provided.

At least one of the available dispersions is selected in accordance with the desired characteristics, e.g., as indicated by a customer order, of the composition to be manufactured. The appropriate quantities of the selected dispersion(s) and the base composition are then mixed at a temperature of from about 20 to about 30 degrees Celsius to produce the final product. More preferably, they are mixed at an ambient or room temperature. One or more aesthetic modifying agents may also be selected, by default or in accordance with the order, and added to the mix in appropriate quantities. Advantageously, because the base composition is pre-mixed, and the additive is provided as a hydrophobic dispersion, this mixing step can be accomplished very rapidly, typically in five minutes or less, making the process suitable for use in manufacturing a large variety of compounds in a short period of time or for manufacturing individual orders on-demand for near-instant delivery.

A particular method for producing a customized composition for at least one of topical, oral, nasal, anal, ophthalmic, and vaginal application, which method is suitable for use in either a distributed Internet-based system or an on-demand kiosk manufacturing system will now be discussed. Fig. 1 is a flowchart generally illustrating the method according to one aspect of the invention. Fig. 2 is a block diagram of a system for implementing the method. The system may be a remotely located manufacturing facility 30 which receives customer orders, e.g.,

through the Internet, or may be housed within a suitable kiosk to provide on-demand manufacturing and delivery. Such a kiosk may be located in a point-of-sale establishment, such as a department store. Alternatively, the kiosk or manufacturing facility may be integrated into a pharmacy. This configuration permits customer orders to be entered by a doctor on behalf of the customer, e.g., through an appropriate Internet web-site. The ordered composition will then automatically be produced at the pharmacy for subsequent pick-up by the customer.

Turning to Figs. 1 and 2, at a first location, initially (a) a base composition comprising a rheology modifying agent and water; (b) a plurality of dispersions; and (c) adjuvants are provided at a first location, generally the manufacturing site. (Step 10). The adjuvants may include one or more aesthetic modifying agents may also be provided. The base composition, dispersions, and adjuvants are provided in reservoirs 32, 34, 36 housed within the manufacturing facility 30 and connected via appropriate conduits 32a, 34a, 36a to a dispensing unit 38. Dispensing unit 38 is a configured to dispense measured amounts of selected ones of the provided components in response to input control signals 39 produced by a control unit 40, such as a computer-based system with appropriate operating programs stored in memory 44. Appropriate dispensing units and control units will be known to those of skill in the art.

A customer order is received at the manufacturing facility 30 (step 14). The order is received through an appropriate customer interface 46. When system 30 is a manufacturing facility remote from the customer, interface 46 is preferably a two-way Internet connection. When system 30 is a kiosk based-facility, the customer interface 46 will typically comprise a video display unit and an entry system, such as a keyboard or touch-screen. Preferably, prior to receiving the customer order, the customer is provided with an indication as to which dispersions and agents are available. (Step 12).

The customer order specifies desired properties of the composition to be manufactured. The properties may be general attributes which are associated to

specific dispersions and/or adjuvants by the control unit 40 in accordance with preprogramed database. Alternatively, the properties may correspond directly to the available dispersions and adjuvants. The implementation depends on the expected sophistication of the customer. Once an order has been received, particular dispersions and adjuvants are selected in accordance with the properties specified in the order (step 20). Preferably, the order passes through a verification process, which may be before and/or after the selection step. During verification, the order is checked to make sure that appropriate materials are available to produce the ordered composition(step 16) and that when the selected dispersions and adjuvants are compatible with each other (step 22). If an error is detected, it is communicated to the customer (step 18) and the customer is asked to enter a corrected order. Alternative formulations may also be suggested to the customer prior to receiving an updated order.

Finally, appropriate quantities of the base composition and the selected dispersions and adjuvants are determined, e.g., in accordance with data-tables stored in the memory 44. The control unit 40 then generates appropriate control signals to instruct the dispensing unit 38 to dispense the determined quantities of compounds from the reservoirs 32, 34, 36 and pass them into a mixer 42. The mixer is activated by the control unit 40 for a short period of time to thereby produce the customized product (step 24) which is then packaged and delivered to the consumer, e.g., through the mail or by dispensing it from the kiosk. Because the mixing step 24 is a relatively short procedure, mixing may be performed directly in the container used to dispense the compound.

According to yet a further aspect of the invention, particularly well suited for the kiosk-based system, but also applicable in an Internet-based environment, various order combinations of dispersion and/or adjuvants (i.e., order properties) may be suggested to the customer. The suggestions may be in accordance with customer profile information, such as skin-type, hair and eye color, age, gender, as well as various other physiological parameters and attributes. Suggestions may

also make use of information gathered from prior orders or other sources. The suggestions may be an aid to help the customer directly indicate the dispersions, water soluble active agents, and/or adjuvants which are to be added. Alternatively, the suggestions may indicate general properties, without regard to the specific components to be added, which components are identified by the control unit 40 during order processing.

The customer profile information can be entered directly by the customer (or a customer service agent) into a kiosk machine or Internet web interface. Alternatively, profile information can be entered onto an order form which is subsequently scanned into or otherwise entered into the system. In yet a further embodiment, an electronic image of the customer, possibly along with other biometric and physiological measurements, is entered into the system and processed to generate a basic user profile. In addition, suggestions may also be made in accordance with environmental factors, such as the time of year, local weather, and the geographic region the customer is in. For example, if a kiosk is located in the North East during winter, the system may suggest that the customer add a moisturizer. If the kiosk is located in Florida during June, the system may suggest the addition of a sunscreen.

In one embodiment of the invention, the user is shielded from selecting the particular dispersions, etc., which are added to the custom compound. Instead, the user profile information and general property selections made by the user are used to determine the overall composition of the compound. In this embodiment, the processing flow is generally simplified since the control unit 40 can ensure that the dispersions, water soluble active agents, and/or adjuvants which are selected to produce the desired composition properties are available and are compatible with each other. Fig. 3 is a flowchart generally illustrating the method according to this aspect of the invention. As shown, the various source materials are first provided. (Step 300). Next, the customer profile information is received, e.g., from the customer, from a customer database, through a customer profile generation sub-

routine receiving input from a digital camera, etc. (Step 302). The customer order is then received, perhaps after various compound properties are suggested to the customer in accordance with an analysis of the user profile. (Step 304). In accordance with the composition properties indicated in the customer order and the customer profile, appropriate dispersions, water soluble active agents and/or adjuvants are selected and appropriate quantities to use are determined. (Step 306). Finally, the appropriate quantities of the selected materials are dispensed and mixed. (Step 308). The final product is then packaged and delivered to the customer.

Customer profile data, prior ordering history, and other information may be stored in an appropriate database and retrieved, e.g., based on a customer name or ID, for use in processing subsequent orders. If system 30 is a kiosk-based system, preferably a secondary data interface 48 is provided to permit customer profile information and additional data to be accessed by the kisok, for the kiosk status to be monitored from a remote site, and for the kiosk to send information messages to an appropriate party, e.g., indicating that certain of the reservoirs need refilling or service. It should be appreciated that while the kiosk systems are stand-alone units, some or all of the data processing and decision making requirements may be off-loaded from the kiosk to a centralized server accessible through the secondary data interface 48.

The following examples are intended to describe the present invention without limitation.

Examples 1-3

These examples demonstrate the flexibility of the system to produce multiple product forms from the same base ingredients if needed. Serum, lotion, and cream base compositions having the formulations in Table 1 below were prepared as follows. Deionized water (A) and Germazide MPB were mixed. Structure Zea was sprinkled into the solution. Carbopol 940 was added and the solution was mixed. Triethanolamine and deionized water (B) were added and the solution was mixed to form the cosmetic base composition.

Table 1

Ingredient	Percentage Weight (based upon 100% total weight of cosmetic base)		
	Example 1 Serum Base	Example 2 Lotion Base	Example 3 Cream Base
Structure Zea[1]	0.75	1.50	3.00
Germazide MPB[2]	1.50	1.50	1.50
Carbopol 940[3] 2% aqueous solution	7.50	15.00	30.00
Triethanolamine (99%)	0.21	0.43	0.86
Deionized water (A)	85.00	78.00	63.90
Deionized water (B)	QS	QS	QS

[1] - S e Zea is a hydroxypropyl distarch phosphate and is available as from Nat arch and Chemical Co. of Bridgewater, NJ.

[2] - C zide™ MPB is a mixture of phenoxyethanol, chlorphenesin, glycerin, meth ben, and benzoic acid and is available from Collaborative Laboratories, Inc. Setauket, NY.

[3] - C 1940 is available from Goodrich Specialty Chemicals of Cleveland, OH. The the serum, lotion, and cream bases were about 6.67, 6.17, and 6.2, resp .

Example 4

This example demonstrates how an oil soluble active can be inco d into the base giving a surfactant free product. A moisturizing lotion for dry h sunscreens having the formulation of Table 2 below was prepared by mix ngredients with either a paddle blade or propeller mixer or with hand mix a spatula or other similar device.

Table 2

	gredi t	Percentage Weight (based upon 100% total weight of composition)
Cream I	ample 3	75.00
Solareas		25.00

[4] - ease™ is a mixture of ethylhexyl methoxycinnamate, butyl met ethane, cyclomethicone, phospholipids, and water and is ava Collaborative Laboratories, Inc. of East Setauket, NY.

Example 5

This example demonstrates how the product in Example 4 can be sup[illegible]ted with a water soluble aesthetic modifying agent. A moisturizing gel loti[illegible]normal skin having the formulation of Table 3 below was prepared by mix[illegible]e ingredients either with a propeller or paddle blade mixer or with hand mix[illegible]h a spatula or other similar device.

Table 3

[illegible]ngredient	Percentage Weight (based upon 100% total weight of composition)
Lotion i[illegible] [illegible]mple 2	60.00
Solareas[illegible]	15.00
Seamolli[illegible]	25.00

[5] - [illegible]lient™ is a mixture of water, algae extract, chlorphenesin, propylene gly[illegible]d hydroacetate, and phenoxyethanol and is available from Co[illegible]ratories, Inc. of East Setauket, NY.

Example 6

This example shows an example of a formulation containing an oil dis[illegible]f an organic sunscreen. An oil-free moisturizer for oily skin having the for[illegible]3 4 below was prepared by mixing the ingredients either with a pro[illegible]ade mixer or with hand mixing with a spatula or other similar dev[illegible].

Table 4

Ingredient	Percentage Weight (based upon 100% total weight of composition)
Lotion B. of Example 2	80.00
Solarease	15.00
Deionize Wa	5.00

Example 7

This is an example of a cream moisturizer containing a variety of different oil dispersions of aesthetic modifying agents. A cream moisturizer having the formulation of Table 5 below was prepared by mixing the ingredients with either a propeller paddle blade mixer or with hand mixing with a spatula or other similar device.

Table 5

Ingredient	Percentage Weight (based upon 100% total weight of composition)
Cream B. Example 1	60.00
AM500[6]	10.00
AM600[7]	10.00
AM200[8]	15.00
Deionize	5.00

[6] – /) is a mixture of water, petrolatum, and cyclomethicone and is available fror [illegible]borative Laboratories, Inc. of East Setauket, NY.

[7] – / is a mixture of water, cyclopentasiloxane, cyclomethicone phospholipids, and [illegible]hicone/vinyl dimethicone polymer and is available from Collaborative Labo[illegible]ies, Inc. of East Setauket, NY.

[8] – / [illegible] is a mixture of water, cyclopestasiloxane and phospholipids and is avai[illegible]om Collaborative Laboratories, Inc. of East Setauket, NY.

Example 8

This example shows the compatibility of the system with liposome deliv[illegible]ystems. A dry skin moisturizer having the formulation of Table 6 below was [illegible]ed by mixing the ingredients either with a propeller or paddle blade mixer or v[illegible]l mixing with a spatula or other similar device.

Table 6

Ingredient	Percentage Weight (based upon 100% total weight of composition)
Cream L[illegible] Example 3	46.95
Frescola [illegible][9]	0.05
Solareas [illegible]	15.00
AM600	8.00
SanSurf [illegible]ula[11]	20.00
AM500	8.00
Vitamin [illegible]ipo[illegible]es[12]	0.50
Germaz[illegible]3	1.50

[9] - F... t Type M... is menthyl lactate and is available from Haaram & Reimer Cor... ...ringfield, NJ.

[10] - ...ease II ... is a mixture of ethylhexyl methoxycinnamate, butyl met... ...ben...ylr... ...ane, cyclomethicone, phospholipids, and water and is avai... ...om Coll...rative Laboratories, Inc. of East Setauket, NY.

[11] - ...C... end... ... is a mixture of cyclopestasiloxane, a propylene glycol based extr... ...ale...dula... ...d is available from Collaborative Laboratories, Inc. of East Seta... ...NY.

[12] - ...in A & E ...iposomes is a mixture of water, phospholipids, tocopheryl acet... ...l re...nyl ...mitate and is available from Collaborative Laboratories, Inc. of E... ...uk..., N...

Examples 9 and 10

These examples show the compatibility of creams and lotions con... water soluble active polymers with dispersions of aesthetic modifying age... ...ear... and ...tion moisturizers having the formulations of Table 7 below wer... ...red... ...y ... ...ing the ingredients either with a propeller or paddle blade mix... ...th... and ...ring with a spatula or other similar device.

Table 7

[illegible]	Percentage Weight (based upon 100% total weight of composition)	
	Example 9	Example 10
Cream [illegible] Example 3	68.82	-
Lotion [illegible] Example [illegible]	-	80.00
Sansurf Pe[illegible]	5.90	4.00
Satin Fi[illegible]	0.99	0.60
AM600[13]	6.88	4.50
Advanc[illegible]tu[illegible]omplex[16]	1.97	1.00
Halosol	1.97	1.00
Sansurf [illegible]	4.42	2.80
Sansurf [illegible]	5.61	3.80
Sansurf [illegible]	3.44	2.30

[13] - [illegible] Pe[illegible] -25 is a mixture of water, petrolatum, and cyclomethicone and is a[illegible] borative Laboratories, Inc. of East Setauket, NY.

[14] - [illegible] mixture of water, phenyl trimethicone, cyclomethicone, dim[illegible] [illegible]ipids, carbomer, and triethanolamine and is available from Co[illegible] [illegible]boratories, Inc. of East Setauket, NY.

[15] - (is a mixture of water, cyclopestasiloxane, cyclomethicone, ph id .imethicone/vinyl dimethicone cross polymer and is available fr aboratories, Inc. of East Setauket, NY.

[17] - . p is a mixture of water, vegepure, cyclomethicone, dimethiconol, and o ds and is available from Collaborative Laboratories, Inc. of East Set Y.

[18] - . MP is a mixture of water, perfluoropolymethylisopropylether, and ph d. s available from Collaborative Laboratories, Inc. of East Set Y.

[19] - S xture of water, phenyl trimethicone, and phospholipids and is av orative Laboratories, Inc. of East Setauket, NY.

Example 11

skin sunscreen moisturizer having the formulation of Table 8 be mixing the ingredients either with a propeller or paddle blade mi h ixing with a spatula or other similar device.

Table 8

	Percentage Weight (based upon 100% total weight of composition)
Cream	70.00
Solare	25.00
Mustard -25 (Natunola)[20]	2.50
Deioniz	2.5

20

[20] - can R-25 is water, white mustard (brassica alba) extract and is av[illegible] anola of Nepean, Ontario, Canada.

Example 12

[illegible]y skin sunscreen moisturizer having the formulation of Table 9 belo[illegible] l by mixing the ingredients with a propeller mixer.

Table 9

	[illegible]nt	Percentage Weight (based upon 100% total weight of composition)
Cream B[illegible]	[illegible] 3	70.20
Frescol[illegible]		0.05
Solarea[illegible]		25.00
Mustard		2.50
Dow Cor	[illegible]d[21]	0.75
Germaz[illegible]		1.50

[21] - [illegible]403 Fluid is a mixture of dimethicone and dimethiconol and is av[illegible] [illegible] Corning Corp. of Midland, MI.

Examples 13-16

[illegible] example shows the ability to produce var[illegible] [illegible]ms without oil tha[illegible] extracts of oil absorbing materials. Oil-free m[illegible]isturizers having the[illegible] Table 10 below were prepared by mixing the ingredients either

wit[illegible] paddle blade mixer or with hand mixing with a spatula or other sim[illegible]ce

Table 10

	Percentage Weight (based upon 100% total weight of composition)			
	Example 13	Example 14	Example 15	Example 16
Lotion B[illegible]	85.00	85.00	83.30	73.30
Solareas[illegible]	10.00	10.00	10.00	10.00
Satin Fi[illegible]	-	-	-	10.00
Pepperm[illegible]	0.20	-	-	-
Frescola[illegible]	-	0.20	0.20	0.20
Germaz[illegible]	-	-	1.50	1.50
Celluflo[illegible]	-	-	5.00	5.00
Deionize[illegible]	4.80	4.80	-	-

22 - [illegible] 25 is cellulose acetate and is available from Collaborative Lab[illegible] of Setauket, New York.

Examples 17 and 18

[illegible] in moisturizing creams and lotions having the formulations in Tab[illegible] prepared by mixing the ingredients either with a propeller or pad[illegible] with hand mixing with a spatula or other similar device.

Table 11

	ngre	t	Percentage Weight (based upon 100% total weight of composition)	
			Example 17	Example 18
Lotion	Ex	2	-	63.20
Cream	Ex	3	63.20	-
Frescol	MI		0.05	0.05
Solarea			25.00	25.00
Mustar	ar	nola)	2.50	2.50
Dow C	10	l	0.75	0.75
Sansur	icor	SFE	7.00	7.00
Germa	B		1.50	1.50

Examples 19-21

ns having the formulations in Table 12 be w ere prepared by mi ing nts either with a propeller or paddle blad mixer or with hand mi h a la or other similar device.

Table 12

	[illegible]	Percentage Weight (based upon 100% total weight of composition)		
		Example 19	Example [illegible]	Example 21
Lotion [illegible]	Exa[illegible] 2	80.00	80.00	80.00
Sansurf [illegible]	ol V	20.00	-	10.00
Sansurf [illegible]	[illegible]	-	20.00	10.00

[23] - Cre[illegible] ol W is a mixture of water, stearyl heptanoat[illegible] cyclomethicone, and [illegible]l, and is available from Collaborative Laborat[illegible]s, Inc. of East Set[illegible] Y.

[24] - La[illegible]n is a mixture of water, lanolin, cyclomethicone, PEG-4, and phe[illegible]ls [illegible] is available from Collaborative Laborato[illegible] Inc. of East Set[illegible] .

Example 22

A [illegible]rolatum spray having the formulation in Tab[illegible] 13 below was pre[illegible] mix the ingredients with either a propeller or paddle blade mixer or wi[illegible] stir[illegible]th a spatula or other similar device. This pro[illegible]t can be used to pro[illegible] rie[illegible]n on the skin.

Table 13

	edi	Percenta e Weight (based upon 100% tota weig t f composition)
Lotion	Exa 2	1 .00
Sansuri	um-	25.00
Germa		1.0
Deioni		0

Examples 23 and 24

nsive moisturizing creams having the formulations in Table 14 be pre d by mixing the ingredients either wi a propel or paddle bl or hand mixing with a spatula or other si ar device

Table 14

	edi	Percentage Weight (based upon 100% total w ght f composition)	
		Example 23	mple 24
Cream	xa 3	70.00	0.00
Advanc	re plex*	1.00	5.00
Deioniz		29.00	25.00

ce isture complex is a mixture of glyce m PCA, u e quaternium 51 and sodium hyalur

Examples 25-28

protecting moisturizing creams having the formulations in Table

15 red by mixing the ingredients either with a propeller or paddle

bla or hand mixing with a spatula or other similar device.

5

Table 15

		Percentage Weight (based upon 100% total weight of composition)			
		Example 25	Example 26	Example 27	Example 28
Cream I	3	70.00	70.00	70.00	70.00
Dermag		10.00	-		10.00
Advance	plex*	-	10.00		10.00
Sansurf		-	-	10.00	-
Deioniz		20.00	20.00	20.00	10.00

* - isture complex is a mixture of glycer water ium PCA, ure vquaternium-51 and sodium hyaluronat

10 25 u is a mixture of water, p ethicone, per isopropylether, stearamidopropyl dim aric acid, and te, and is available from Collaborative L orate ne. of East Se

15 Examples 29 and 30

examples illustrate that t base c ition e present inv ble with low pH compositions. Lo having

the ... Table 16 below were prepared by mix... the ... ents with a pro...

Table 16

	Percentage Weig... (based upon 100% ... wei... cosmetic base)	
	Example 29 Lotion Base	...mple 30 ...am Base
Carrage...	0.75	1.50
Scleroti...	0.75	1.50
Glyceri...	1.0	2.00
Germazi...	1.5	1.50
Deioniz...	95.0	87.5
Propyle...	-	2.00

The ... base and cream base were about 4.1 ... 3 ... pectively. The ... of the lotion base and cream base we... ou... and 1.012 g/cc ...

Example 31

...example illustrates a cationic base w... is ... tible with cati... ...s and cationic aesthetic modifying a... ...s. ... ...etic base hav... ...n in Table 17 below was prepared as f... ... ...IP60 was spri... ...nized water mix until homogenous ... ...ric acid

wa ...en the solution and adjust the pH to ... 5 ... he specific gra ...netic base was about 1.015 g/cc.

Table 17

	Percentage Weight (based upon 100% total weight ... netic base)
Jaguar ...	...
Deioni...	98....

27 ... is hydroxypropyl guar and is available ... Poulenc of Cr...

Example 32

... eam base having the formulation in Tab... s below ... s prepared a... ...ed water (A), Pure Gel B980, and Ger... de ... ere mixed tog... 940 was added to the soluion and mix... Tri... amine and de... were added to the solution and mixe...

Table 18

	nt	Perc ge h (based upon 100% l w cream base)
Pure G		0
Germa		0
Carbop	ueous)	0
Tietha		3
Deioniz		0
Deioniz		07

28 -) is sodium hydroxypropyl starch phosp ilable from
5 Gr Corporation.

Example 33

is is an example of a cationic gel base. A having the
for le 19 below was prepared as follows. nd Jaguar
10 HP d together. While the deionized water mixture of
Jag HPSCoS was sprinkled into the outer ed formed by
the The solution was mixed.

Table 19

	Perce ge (based upon 100% t .l v f cream base)
Jaguar C	.75
Jaguar H.	375
Deionized	87

[29] - J is guar hydroxypropyltrimonium chlo an ilable from Rh Cranbury, NJ.

[30] - M is hydroxypropyl guar and is availabl Poulenc of Cra.

Example 34

ce and scalp intense protection gel ha ulation in Tabl as prepared as follows. Jaguar C14S a SCOS were mix d added to the deionized water while de water was stir d aloe gel were added to the solution Tween 20, ch... osemary oil were mixed and added t s. Germazide MPB the solution and mixed.

Table 20

		Pe (based upon 100	f cream base)
Solarcat			.)0
Aloe Gel			)0
Tween 2(			15
Chamon			5
Rosemary			5
Germazi			0
Deionize			25

31 - a mixture of water, ethylhexyl xyl ate, butyl
5 met ethane, cyclomethicone, stearam yl thylamine,
stea nethylamine stearate, and balm m s available
fro abor tories, Inc. of East Setauket,

Example 35

10 example shows a cationic base ain dispersion
sun sition having the formulation in Ta be s prepared
by n ients either with a propeller or padd with hand
mix or other similar device.

15

Table 21

		Pa ge W t (based upon 10 l w	of cream base)
Cosmet	ple 4	.00	
Catezon		.00	
Germaz		50	
Deioniz		.50	

32 OMC is a mixture of ethylhex the namate and
5 ste: limethylamine stearate and is av fr ollaborative
Lab f East Setauket, NY.

ats, publications, applications, m s mentioned
her corporated by reference.
10 v riations of the present inventi ge emselves to
the in light of the above, detailed d m. uch obvious
var e full intended scope of the app the

W

A composition for topical, o... ...ar ophthalmic, or v... ...mprising (a) a base composition c... (i) a rheology m... ...ier ...nd (ii) water; and b) at least one dispersio... ...g... ...ended particles o... ...e agent, a hydrophobic adju... ...or ...ation thereof, w... ...on is substantially free of c... ...s... ...etants and the s... ...ve a diameter less than abou...

A method of preparing a com... ...or ...al, oral, nasal, a... ...ginal application, the metho... ...ng ...ing a base composition comprisi... (i) a rheology m... ...ier ...d (ii) water; and at least one dispersion comp... ...per... ...d particles of a hy... ...ent, a hydrophobic adjuvant, o... ...ati... ...hereof, wherein th... ...red is substantially fr...e of c... ...g... ...etants and the su... ...ve a diameter less than abou...

A method of preparin... a com... ...or ...l, oral, nasal, a... ...ginal application, the metho... ...ng ...ing (a) a premanufactured b... ...ite ...omprising (i) a rheology m... ...ier ...d (ii) water; and b) at least one dispersio... ...g... ...nded particles o... ...e agent, a hydrophobic adju... ...omb... ...ion thereof, w... ...on prepared is substantially fr... ...ly ...urfactants and t... ...s have a diameter less than a... ...or

1 e method of claim 3, wherein sit n comprises
2 suspe ing a diameter of from about 5 00 nm.

1 e method of claim 3, wherein n nprises oil.

1 e method of claim 5, wherein n within oil
2 dro

1 e meth d of claim 6, where dr plets have a
2 diam 250 to about 500 nm.

1 e method of claim 6, wherein et nprise one
2 or als.

1 e method of claim 6, wherein et ve a charge
2 as d ential measurements.

1 e meth d of claim 3, wherein n repared by
2 hig h shear mixing, or a combina f.

1 e method of claim 3, wherein n repared by
2 ultr r microfluidization.

1 e meth d of claim 3, wherein is rformed by
2 prop mixing, or sweep blade mixi

1 e meth d of claim 3, where g erformed
2 ma

1 e meth d of claim 3 wherei g erformed
2 wit

1 e meth d of claim 3, wherein rmed at a
2 ten t 15 to about 30°C.

1 he method of claim 15, wherein [illegible] rformed at a
2 ter[illegible] ut 20 to about 30°C.

1 he method of claim 3, wherein [illegible] erformed at
2 am[illegible]

1 composition for topical, oral, [illegible] hthalmic, or
2 va[illegible] ared by the method of claim 3.

1 method for producing a custom [illegible] for at least
2 on[illegible] l, anal, ophthalmic, and vagin[illegible] mprising the
3 ste[illegible]
4 g at a first location (a) a base [illegible] mprising a
5 rhe[illegible] ent and water and (b) a plurali[illegible] s, the base
6 co[illegible] ared at a second location, [illegible] comprising
7 sus[illegible] hydrophobic active agent, a [illegible] uvant, or a
8 co[illegible]
9 a customer order at the first loc[illegible] roperties of
10 a d[illegible]
11 at least one of the plurality of dis[illegible] rdance with
12 the
13 an ambient temperature a quant[illegible] omposition
14 wi[illegible] ected dispersions to form the [illegible] osition.

1 he method of claim 19, further [illegible] ps of:
2 at least one aesthetic modifyi[illegible] st location;
3 and
4 at least one of the plurality of aes[illegible] g agents in
5 acc[illegible] mer or[illegible]

6 ...mixing comprising the step of ...ity of base
7 co... ...ntities of the selected dispe... ...ies of the
8 sel... ...ing agents to form the custom...

1 ...e method of claim 19, wherein t... ...n is remote
2 fro...

1 ...method of claim 19, wherein t... ...originates
2 at a ... the first location.

1 ...e method of claim 19, wi... ...mer order
2 ori... ...ation.

1 ...e method of claim 19 further ... ...teps of:
2 ...g to the customer properties of ... ...spersions
3 ava... ...on; and
4 ...ti... the properties which can be s... ...stomer to
5 the ... ...e

1 ...e method of claim 19, where... ...tep further
2 con... ... the selected dispersions and ...sition are
3 con... ...r.

1 ...method of claim 25, furth... ...step of
2 rej... ...response to a determination of inc...

1 ...e method of claim 25, furth... ...step of
2 pro... ...lications to the custom... in resp... ...mation of
3 inc...

1 ...method of claim ..., furth... ...step of
2 pro... ...customer prior to t... receiv... ...nce with
3 env...

1 ... method of claim 19, where... mental factors
2 ing... late local humidity, and geo...

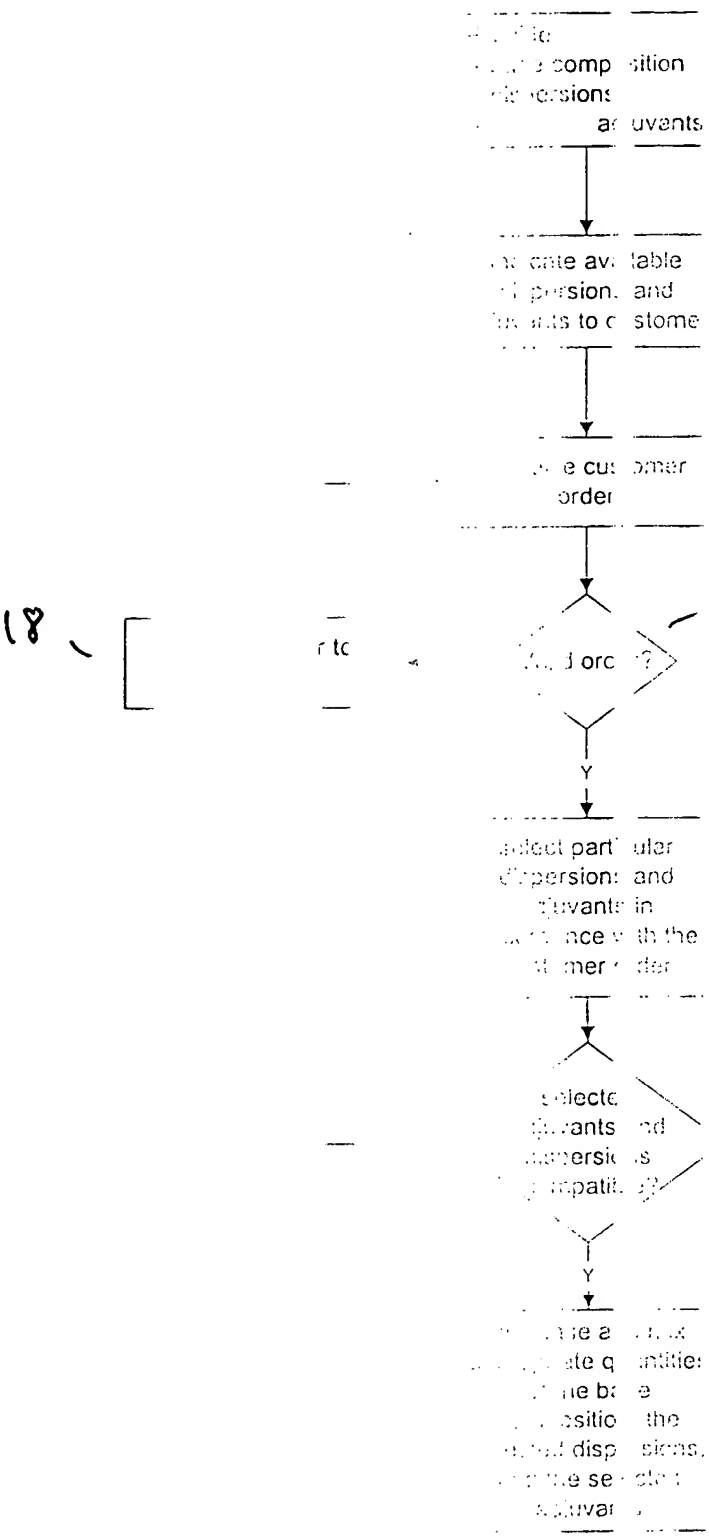
1 ... d for producing a custo... for at least
2 on... na... ophthalmic, a... vagi... ...prising the
3 ste...
4 ... di... rst location:
5 ... omposition comprising ... ing agent,
6 ... ity of dispersion, each co... d particles
7 of ... ive... hydrophobic adjuvant... ...thereof, and
8 ... ne aesthetic modifying
9 ... tin... ore of the plu... lity of c... ...dance with
10 a c... d
11 ... ambient temperature the ba... the selected
12 dis... as... ected aesthetic modifyin... ...customized
13 co...

1 ... ...of claim 34, whe... ...e selected
2 aes... ...ected in accordance wi... ...er.

1 ... d for producing a custo... for at least
2 one... na... ophthalmic, a... vagi... ...prising the
3 ste...
4 ... ri... e composition comprisin... ...ing agent
5 and... oc...
6 ... ...e composition;
7 ...or... the base composition to a s...
8 ... ...e composition at the s...

9 ... ...ality of dis...ersions ...lication, each
10 disp ... ...particles of a ... ... agent, a
11 hyd ..., ...ion thereof;
12 ... ...one of the plu...lity of ...
13 ... ... temperatu...e a qua... ...mposition
14 with ... ...persions to f...rm the ... ...osition.

1 ... ...ting to...ical, o... ...halmic or
2 vagi ... ...prepared by:
3 (...composit...n com...
4 ...rheolo...y modi... ...
5 ...water; and
6 (...least one disp...sion co... ...d particles
7 of a ... ...hydrophobic adjuvant... ...n thereof,
8 ... ...ion is substa... ...mulsifying
9 surf... ...have a diamete... ...00 nm.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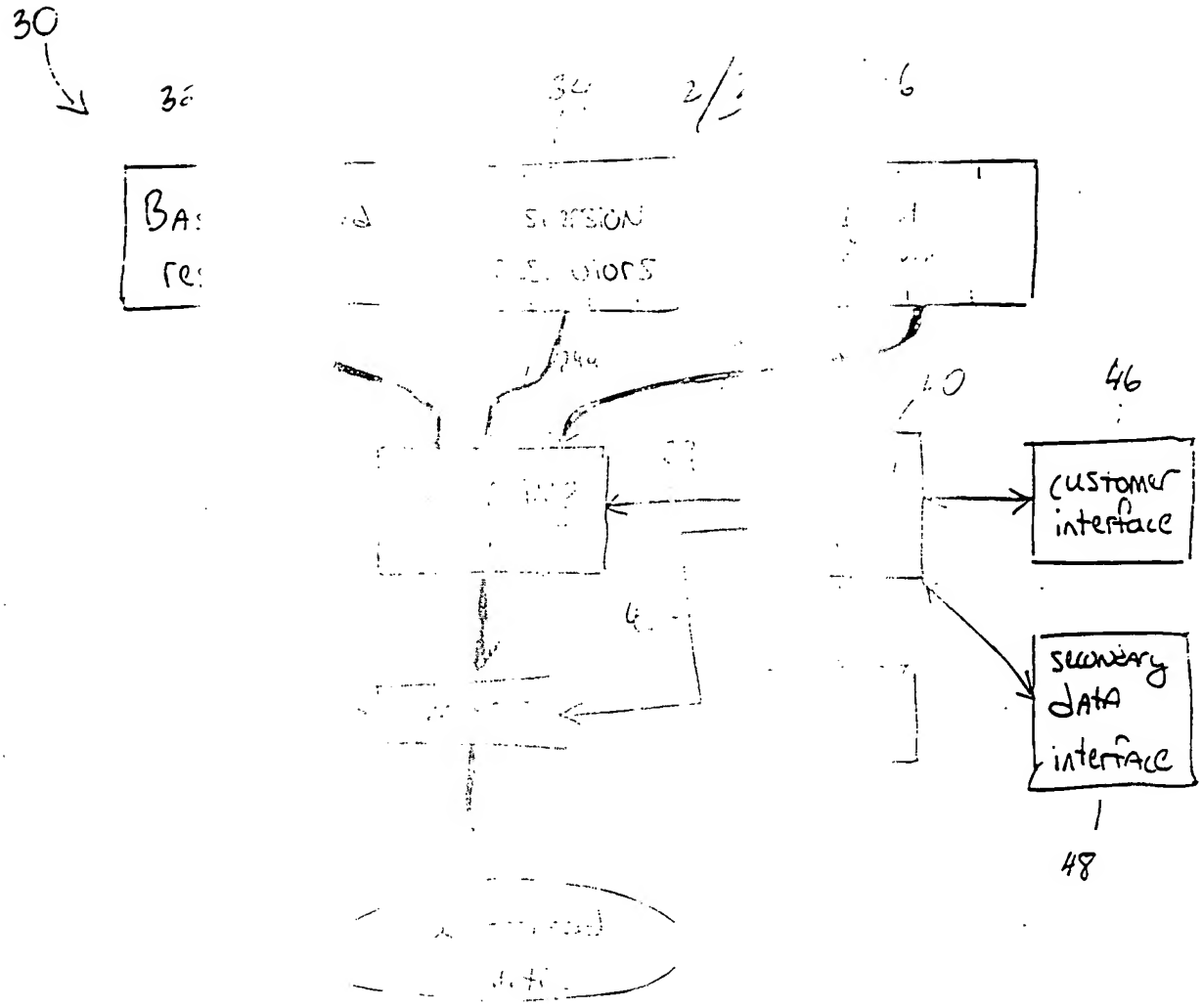
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secondary data interface
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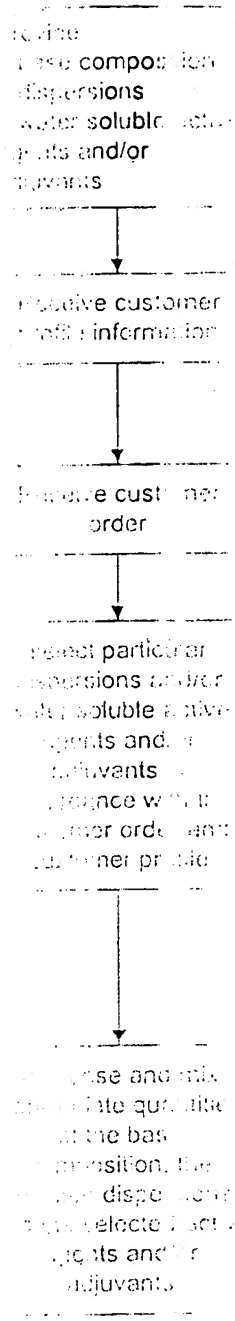
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port

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20 December 2001

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(54) Title: SURF TO ME S CH RATION THEREOF

(57) Abstract: for pi or vaginal application com-
prising a base c ing prising active agent, a hydrophobic
adjuvant, or a c ing impr d water. The composition is
substantially fre part n about 500 or 1,000 nm.
Another emb ticle co ase composition with the
aforementioned c a prop nce the topical dispersion
is simple and quic ns may omers. Prior to the present
invention, such p Furthe ention is significantly more
efficient *i.e* less c p ons. The present invention
further relates to gw h position of this invention.

ATENT SEARCH REPORT

Application No
03157

A. CLASSIFICATION
IPC 7 A61K

According to International Patent Classification

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US [illegible] (E S)	1-3
P,X	WO 9 [illegible] the	1
X	WO 19 [illegible]	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search
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